

## **β-Blockers decrease cardiac events in major noncardiac surgery**

Auerbach AD, Goldman L. β-Blockers and reduction of cardiac events in noncardiac surgery. Scientific review. JAMA 2002; 287:1435-44.

■ **BACKGROUND** Attempts to reduce serious cardiac events during major noncardiac surgery have traditionally relied on preoperative assessments of risk. In the highest risk patients, cardiac revascularization is often considered to reduce postoperative cardiac events, without much evidence to support its use. Researchers have begun to examine whether β-blockade during the perioperative period could be used in lieu of revascularization to reduce these events. This systematic review summarized what is known about this intervention.

■ **POPULATION STUDIED** The researchers identified 6 publications of 5 randomized, controlled trials, completed after 1980, through a MEDLINE search. Reference lists from relevant articles were reviewed to identify additional studies. These studies evaluated patients who were undergoing elective noncardiac major surgery and who either had known ischemic heart disease or risk factors for ischemic disease. Studies were inconsistent in inclusion or exclusion of patients on long-term β-blocker therapy.

■ **STUDY DESIGN AND VALIDITY** In this systematic review, the authors identified prospective randomized trials but did not evaluate the quality of the trials. The 5 trials used a variety of β-blocker drugs, doses, and dosing schedules. All but 1 study titrated β-blocker therapy before or with the induction of anesthesia to a target heart rate of 70 beats per minute or slower. The β-blocker therapy was continued through the operative period and for a varied time after surgery. No information was presented in the article regarding randomization method or intention-to-treat analysis in the trials.

■ **OUTCOMES MEASURED** All trials reported 1 or more of the following outcomes: myocardial ischemia, myocardial infarction, cardiac death, and all-cause mortality.

■ **RESULTS** Two trials found statistically significant reduction in ischemia with β-blocker therapy, with 1 ischemic event prevented in 2.5 to 6.7 patients treated with a β-blocker (33% vs 73%,  $P < .05$ , number needed to treat [NNT] = 2.5; 24% vs 39%,  $P = .03$ , NNT = 6.7). A third trial found a decrease in ischemia that did not reach statistical significance. The control group in the third trial had a low incidence of ischemia.

Postoperative myocardial infarction (in the 2 trials that evaluated the condition) was significantly reduced with β-blocker therapy. The NNT in these patients was 3.8 and 5.9 (0% vs 17%,  $P < .001$ , NNT = 5.9; 2% vs 28%,  $P < .001$ , NNT = 3.8).

Two trials reported significant reductions in mortality, with NNT of 7.4 and 8.3 (9% vs 21%,  $P = .02$ , NNT = 8.3; 3.4% vs 17%,  $P = .02$ , NNT = 7.4).

In all studies, the benefit of β-blocker therapy was greatest in patients with known coronary artery disease.

### **RECOMMENDATIONS FOR CLINICAL PRACTICE**

Using β-blocker therapy perioperatively reduces myocardial ischemia, infarction, and mortality. Family physicians should recommend and prescribe perioperative β-blocker therapy in patients who meet criteria that put them at higher risk for coronary artery disease. The algorithm and the eligibility criteria described in the article provide specific guidance in implementing the evidence in day-to-day practice.

*Wesley D. Johnson, MD, MSE*

*Neil Korsen, MD*

*Department of Family Practice*

*Maine Medical Center*

*Portland*

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## Angiotensin receptor blockers not equivalent to ACE inhibitors for heart failure

Jong P, Demers C, McKelvie RS, Liu PP. Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2002; 39:463-70.

■ **BACKGROUND** Although, in theory, angiotensin receptor blockers (ARBs) offer improved blockade of the renin-angiotensin-aldosterone pathway over angiotensin-converting enzyme (ACE) inhibitors, their relative effectiveness in the treatment of heart failure remains controversial. This meta-analysis combined all relevant randomized-controlled studies comparing the benefits of ARBs alone or in combination with ACE inhibitors.

■ **POPULATION STUDIED** The authors identified 17 studies comparing ARBs with placebo or ACE inhibitors published before May 2001 through a search of 7 relevant databases. To be included, the studies had to have a treatment duration of at least 4 weeks, include patients with New York Heart Association functional class II to IV, use a randomized, blinded design, and report outcomes of death or hospitalization. Studies were excluded if they were published only as abstracts or in non-peer-reviewed journals, were crossover trials or single-dose studies, included nonrandomized investigational agents, or had other significant validity concerns. Three ongoing, but otherwise relevant, studies were not included.

The 17 trials included a total of 12,469 patients whose mean ages ranged from 56 to 73 years. The trials included 48% to 100% men and 59% to 100% white patients. The proportion of patients with severe heart failure (class IV) varied from 2% to 15% across the studies.

Seven studies compared ARBs with placebo, and 1 included only ACE inhibitor-intolerant patients. Six studies compared ARBs with ACE inhibitors and 6 compared ARBs plus ACE inhibitors with ACE inhibitors alone (2 trials contained 2 arms). Five different ARBs were used: losartan (9 studies), candesartan (3 studies), valsartan (3 studies), irbesartan (1 study), and eprosartan (1 study). The length of treatment varied from 4 weeks to 1.5 years.

■ **STUDY DESIGN AND VALIDITY** The protocol followed guidelines for performing Cochrane reviews. Inclusion decisions were reached by consensus and outcome data were independently extracted by 2 reviewers, with disagreements settled by consensus or third reviewer. Reasons for excluding each article were listed and potential validity concerns of the included articles were addressed. For their primary analysis the authors combined all ARBs regardless of type, dosage, or concomitant ACE inhibitor therapy and compared them with all controls, whether placebo or ACE inhibitors. Subanalyses followed comparing ARBs with placebo, ACE inhibitors, and ARB + ACE inhibitor with ACE inhibitor alone. All data were analyzed based on intention to treat.

This well-done meta-analysis is a valid summary of the current evidence. However, with 3 major ongoing trials, the conclusions may change in the future. The conclusions are limited by assuming a class effect of all ARBs and ACE inhibitors and not evaluating the outcomes with different dosages. In addition, the authors reported a post hoc power calculation for the primary analysis only, making the nonsignificant findings of the subanalyses difficult to interpret.

■ **OUTCOMES MEASURED** The primary outcome was all-cause mortality (evaluated in all 17 trials). The secondary outcome was hospitalization for heart failure, worsening signs and symptoms of heart failure, or complications of heart failure treatment. Hospitalization data were extractable from only 6 of the trials, but these trials contained the most patients (N = 10,031).

■ **RESULTS** No statistical difference in all-cause mortality was found in the primary analysis (odds ratio [OR] = 0.96; 95% confidence interval [CI], 0.75-1.23). There was also no difference in mortality in trials comparing ARBs with placebo only (OR = 0.68; 95% CI, 0.38-1.22), trials comparing ARBs with ACE inhibitors (OR = 1.09; 95% CI, 0.92-1.29), or in trials comparing combined ARBs and ACE inhibitors with ACE inhibitors alone (OR = 1.04; 95% CI, 0.91-1.20). Overall, treatment with an ARB had no effect on the rate of hospitalization due to heart failure. Similar to mortality, 2 of the subanalyses, ARBs vs placebo and ARBs vs ACE inhibitors, showed no difference (OR = 0.67; 95% CI, 0.29-1.51 and OR = 0.95; 95% CI, 0.80-1.13). However, the combination of ARBs with ACE inhibitors reduced hospitalization rates as compared with ACE inhibitors alone (OR = 0.74; 95% CI, 0.64-0.86, NNT = 23 for about 2 years).

### RECOMMENDATIONS FOR CLINICAL PRACTICE

This meta-analysis, combining all relevant trials to date, did not demonstrate a reduction in mortality in patients treated with ARBs for heart failure. Despite this finding, patients unable to take an ACE inhibitor may still receive a benefit if an ARB is substituted. The combination of an ACE inhibitor and an ARB may decrease the overall rate of hospitalization for worsening heart failure, but not mortality. However, studies with dose-adjusted comparisons are required before justifying the added costs and risks associated with combining both medications. Meanwhile, clinicians should continue to use ACE inhibitors as first-line therapy in heart failure and consider ARBs for patients unable to tolerate ACE inhibitors.

James G. Slawson, MD  
Linda N. Meurer, MD, MPH  
Department of Family and Community Medicine  
Medical College of Wisconsin  
Milwaukee  
E-mail: jslawson@mcw.edu

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## Several depression screening tools work equally well

Williams JW, Noel PH, Cordes JA, Ramirez G, Pignone M.

Is this patient clinically depressed? JAMA 2002; 287:1160–70.

■ **BACKGROUND** Depressive disorders are common in primary care, but the optimal approach for diagnosis remains controversial. This information summary compared various depression case-finding instruments suitable for the office setting.

■ **POPULATION STUDIED** This summary included 28 studies of depression case finding instruments with more than 25,000 screened patients drawn from Veterans Affairs clinics, academic practices, health maintenance organizations, and community practices. Given the variety of study settings, the results of the study are probably generalizable to the average family practice. More information about participants' age, sex, ethnicity, symptom severity, and comorbid conditions would allow better assessment of the performance of case-finding instruments in specific groups of patients of particular importance in primary care such as women, patients of color, and the chronically medically ill.

■ **STUDY DESIGN AND VALIDITY** The investigators summarized information from studies that evaluated case-finding instruments in the primary care setting. Using terms featuring *depressive disorder* or *depression*, the authors searched MEDLINE, a specialized depression trial registry, and bibliographies of selected articles for English-language literature published from 1970 to 2000. They included studies with at least 100 subjects, that used instruments with a depression-specific component and low literacy requirements and complexity, and that used a standard interview to make an independent and masked criterion-based diagnosis of depression. Two independent reviewers abstracted the studies and evaluated study quality. If necessary, original authors were contacted for additional information. Established cut points were used to calculate average likelihood ratios, weighted for study precision and 2-phase assessment if applicable. A summary effectiveness score was used to assess for heterogeneity.

Methodological strengths include the thorough search, independent review, and attention to study size and quality. The major weakness was that the "gold standard" interview was not performed in many of the screened patients. The authors did not describe how the quality score was used to select studies for the final analysis or how the effectiveness

score was calculated. In addition, few empirical data were provided on how long the screening tests took to administer in practice.

■ **OUTCOMES MEASURED** The major outcome was the average positive and negative likelihood ratios for each case-finding instrument. Outcomes important in primary care that were not addressed included clinician and patient satisfaction and effects of screening on office flow and patient outcomes.

■ **RESULTS** The 28 published studies evaluated 11 different instruments, including the Beck Depression Inventory, the Zung Self-Assessment Depression Scale, and the Primary Care Evaluation of Mental Disorders. Of these, 15 studies met quality assessment standards and were included in the final analysis. With regard to instrument performance in detecting depression, the median positive likelihood ratio was 3.3 (range, 2.3–12.2), and the median negative likelihood ratio was 0.19 (range, 0.14–0.35). No significant difference was found between screens. However, 4 instruments, including the Beck, demonstrated statistically significant variation across studies, which the authors attributed to either variability of study population or design.

### RECOMMENDATIONS FOR CLINICAL PRACTICE

This study provides fair evidence that depression case-finding instruments perform similarly and fairly well in detecting and ruling out depression with a wide variety of outpatients. Clinicians should thus choose a specific case-finding instrument based on other characteristics, such as ease of use, response format, and the need to screen for other psychiatric diseases. The Patient Health Questionnaire best meets these criteria, with only 9 questions, a simple format and modules for other illnesses. For screening, the single question, "Have you felt depressed or sad much of the time in the last year?" performs well. It should be kept in mind, however, that this study did not address the impact of using case-finding screens on patient flow, the effectiveness of case finding on outcomes from depressive disease, or whether routine screening for depression is merited.

Amrit R. Singh, MD

Warren P. Newton, MD, MPH

Department of Family Medicine

University of North Carolina

Chapel Hill

E-mail: amrit\_singh@med.unc.edu

## Switching antidepressant classes often works in treatment-resistant depression

Thase ME, Rush AJ, Howland RH, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. *Arch Gen Psychiatry* 2002; 59:233-9.

■ **BACKGROUND** Many strategies have been used to manage patients with treatment-resistant major depression. Few controlled trials have prospectively addressed the effects of switching between classes of antidepressant medication. This investigation measured the effects of switching patients with treatment-resistant chronic depression from one class of medication to another.

■ **POPULATION STUDIED** Eligible subjects included 207 outpatients referred from primary care physicians and mental health professionals or who responded to advertising or word of mouth. The patients were between the ages of 21 and 65 years and were diagnosed with chronic major depression according to the DSM-III-R criteria, based on a structured clinical interview. All patients were initially treated and did not respond to 12 weeks of double-blind treatment with either sertraline (at least 50 mg daily) or imipramine (at least 150 mg daily). The authors did not enroll patients with mood and anxiety disorders, psychotic disorders, personality and somatoform disorders, or substance abuse disorders. They also excluded patients who had not responded previously to low doses of sertraline or imipramine (ie, at least 4 weeks of at least 50 mg sertraline or 150 mg imipramine daily).

■ **STUDY DESIGN AND VALIDITY** The study was randomized and double-blinded. Of the 207 nonresponders, 168 (81%) were enrolled and switched to the alternate antidepressant for an additional 12 weeks of follow-up. Psychotherapy was continued during the study only if it had been ongoing for at least 3 months before intake. In both phases of the study, imipramine was increased to a maximum of 300 mg daily and sertraline was increased to a maximum of 200 mg daily if tolerated. Drug doses were gradually increased so that the maximum dosage of either drug could be reached by the 6th week.

All clinical ratings were completed by a blinded independent evaluator. The study lacked a placebo control group; thus, the effects of placebo on depression could not be evaluated. A placebo control group was not used in this study because of concerns about withholding active treatment from chronically depressed patients.

■ **OUTCOMES MEASURED** Outcomes measured included the 24-item Hamilton Rating Scale for

Depression and the Clinical Global Impressions Severity and Improvement scales. Other outcomes related to chronic depression such as absence from work, physician visits, acute and chronic hospitalizations. Other social and economic issues were not measured in this study.

■ **RESULTS** Switching from sertraline to imipramine (mean dosage, 221 mg/day) and from imipramine to sertraline (mean dosage, 163 mg/day) resulted in clinically and statistically significant improvements. Using intention-to-treat analysis, switching medications resulted in a higher response rate in the sertraline group (60% in the sertraline group vs 44% in the imipramine group,  $P = .03$ ). More patients whose depression did not improve with imipramine subsequently responded favorably to sertraline as compared with the converse. Attrition related to side effects was higher in patients treated with imipramine (41% vs 30%,  $P = .045$ ) and was similar to the dropout rate of other studies (number needed to treat = 9). Although the initial antidepressant response rate was favorable, after the switch of medications only 32% of patients in the sertraline group and 23% in the imipramine group achieved full remission. About half of the initial responders had significant residual depressive symptoms after 12 weeks of pharmacotherapy.

### RECOMMENDATIONS FOR CLINICAL PRACTICE

About half the patients who do not respond to an initial trial of either a selective serotonin reuptake inhibitor (SSRI) or a tricyclic antidepressant will respond to some degree when switched to a medication from the other class. Ultimately, however, only about 20% to 30% of these patients will achieve full remission after 16 weeks of therapy with the new agent. Initial nonresponders to a tricyclic antidepressant were more likely to respond to the SSRI than nonresponders to the SSRI who were switched to a tricyclic agent. Switching across classes is an option but not a requirement in treating patients with resistant major depression.

*Velukumari T. Nanjagowder, MD  
Department of Family Practice  
Thomas Jefferson University  
Philadelphia, Pennsylvania  
E-mail: ngowder@cs.com*



## Screening decreases breast cancer-specific deaths but not all-cause mortality

Nystrom L, Andersson I, Bjurstram N, et al. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet* 2002; 359:909-19.

■ **BACKGROUND** A previous meta-analysis of 4 Swedish randomized controlled trials demonstrated a reduction in breast cancer mortality but not overall mortality with screening mammography.<sup>1</sup> Critics raised concerns about the study methods and validity of the results. This article reported the results from a new meta-analysis of the Swedish studies with longer follow-up. The authors also defined and defended their methods in detail.

■ **POPULATION STUDIED** The 4 Swedish trials were combined to include a study group of 247,010 women aged 40 to 74 years. A total of 129,750 women received mammography and 117,260 were controls. Some trials randomized individuals, whereas others used a quasirandomization method in which clusters of people were randomized by day of birth or geographic area. Women were excluded if they had a diagnosis of invasive cancer prior to randomization. Overall, 4001 women younger than 40 years and 14,959 women older than 75 years were excluded.

■ **STUDY DESIGN AND VALIDITY** The meta-analysis combined the results of 4 Swedish randomized control trials and extended the follow-up from previously reported data. The primary end point was breast cancer mortality as recorded in the Swedish Cause of Death Registry. The original files were obtained and records were linked to the 6 regional oncologic centers as well as the Swedish Cause of Death Register. The end date of follow up was December 31, 1996. Two statistical models were developed by the researchers to allow for better comparison between different trials.

This study is a follow-up to a meta-analysis published in 1993. The authors attempted to clarify criticisms surrounding their methods and randomization techniques while adding additional supporting data up to and including 1996. Ultimately the authors dismissed the previous criticisms as misleading and scientifically unfounded. A potential flaw was that some of the comparison groups offered mammography screening, which could have diluted the apparent overall beneficial effect of mammography. To address this weakness, the authors developed an "evaluation model" that ignored breast cancer deaths among women whose diagnosis was made after the first mammography screening round of the control group. The results from this type of reanalysis demonstrated the "best case scenario." If these same breast cancer deaths are not ignored, then mammography screening appears less beneficial.

■ **OUTCOMES MEASURED** The primary outcome measured was long-term effects on mortality, including age-specific and trial-specific effects. Mortality was separated into breast cancer mortality, cumulative breast cancer mortality by age group, and total mortality.

■ **RESULTS** Using the "evaluation model," breast cancer mortality was reduced 21% with invitation to mammography screening (relative risk [RR] = 0.79, 95% confidence interval [CI], 0.70-0.89). This risk was similar across all age groups. The cumulative breast cancer mortality per 100,000 women was decreased in each trial and at each age of entry when screening was started. The absolute reduction for all women aged 40 to 74 years at entry was 136 per 100,000 at 18 years after randomization. Overall, total mortality was not affected by mammography screening (RR = 0.98, 95% CI, 0.96-1.00), but the 50- to 59-year and 60- to 69-year age groups did show a mildly significant benefit (RR = 0.95, 95% CI, 0.92-0.98, and RR = 0.94, 95% CI, 0.91-0.97, respectively).

### RECOMMENDATIONS FOR CLINICAL PRACTICE

This study confirms screening mammography's role in the reduction of breast cancer-related deaths. The effects of mammography on breast cancer mortality reduction have persisted after long-term follow-up of previously supportive data. These effects are age dependent and seem to benefit women aged 55 to 69 years. What this analysis failed to demonstrate, however, was a significant reduction in overall mortality. That is, despite being diagnosed with breast cancer through mammography, these women still have a similar risk of dying from any cause compared with those who were not screened. Until legitimate data are presented that dispute the long-term benefits of breast cancer screening, however, mammography persists as a valuable tool in reducing mortality related to breast cancer. The National Cancer Institute continues to recommend screening mammograms every 1 to 2 years starting at age 40.<sup>2</sup>

*Chris Farmer, MD*

*Kevin Y. Kane, MD, MSPH*

*Department of Family Practice*

*University of Missouri-Columbia*

*E-mail: FarmerC@bealhb.missouri.edu*

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## Several options effective for postherpetic neuralgia

Alper BS, Lewis PR. Treatment of postherpetic neuralgia: a systematic review of the literature. *J Fam Pract* 2002; 51:121–8.

■ **BACKGROUND** Postherpetic neuralgia (PHN) is the most common complication of herpes zoster, especially in older patients, and can last weeks to years. This study evaluated the literature to determine the most effective treatments for PHN.

■ **POPULATION STUDIED** Patients in the included studies were a mean age of 71 years (range, 16–90 years). Most of the patients had had PHN for more than 1 year.

■ **STUDY DESIGN AND VALIDITY** This study was a well-done systematic review of English language, randomized controlled trials evaluating treatments for PHN with patient-relevant outcomes and evaluation periods of more than 24 hours. After a qualitative assessment of the 186 identified studies, 27 were included for methodologic review. Methodologic quality of the studies was rated independently by the authors using the 5-point Jadad scale, which is a well-evaluated validity checklist addressing randomization technique, allocation concealment, blinding, and accounting of dropouts. Most of the trials were found to be of good quality, receiving a Jadad score of 4. Trials scoring only 1 point were excluded with 2 exceptions: both were not double-blinded but were otherwise methodologically strong.

Several important items are not evaluated by the Jadad scale and may limit the validity of some of the included studies. Failure to analyze patients in the groups to which they were randomized (intention-to-treat analysis) may mean the results will not translate to the “real” world, lack of washout periods in short crossover trials may mute positive results, and potentially significant baseline differences between study groups may also bias results.

Because most of the patients in the included studies had PHN for more than 1 year, the results of the review may not apply to patients with a shorter duration of symptoms who are more commonly seen by a primary care physician.

■ **OUTCOMES MEASURED** Outcomes measured were PHN pain resolution, severity, and effect on quality of life.

■ **RESULTS** The strongest evidence in this review supported the use of tricyclic antidepressants for the

treatment of PHN, with 1 patient responding for every 2 to 3 who were treated (number needed to treat [NNT] = 2–3). Common side effects were dry mouth, drowsiness, and constipation. Amitriptyline was the best-studied antidepressant, at a dose of 75 mg nightly. Gabapentin 1200 mg 3 times daily was effective in a single, large placebo-controlled trial with an NNT of 3.2 for the outcome of moderate or better pain relief and 13.9 for the outcome of no pain during the 8th week of treatment. For every 2 patients treated with gabapentin, 1 had somnolence, dizziness, or ataxia. Controlled-release oxycodone 20 mg every 12 hours was effective in a crossover trial with an NNT of 2 for pain relief and common side effects of constipation, nausea, and sedation. Topical capsaicin 0.075% cream applied 4 times daily showed a trend toward effectiveness in a large trial and greater effectiveness in a smaller trial with an NNT of 2 for pain relief, although skin reaction was common and caused significant patient dropout from the study. The ability to blind these studies was difficult because of the stinging effect of the capsaicin. Intrathecal methylprednisolone plus lidocaine was highly effective for achieving good or excellent results (pain relief > 50%) in patients with longstanding PHN refractory to multiple conventional therapies, with an NNT of 2 and no reported adverse effects.

Other approaches have not been well studied: lidocaine patch, benzydamine cream, vincristine and dimethylsulfoxide iontophoresis, tramadol, and bupivacaine sympathetic block. Dextromethorphan, memantine, acyclovir, lorazepam, fluphenazine, and acupuncture do not appear to be effective in the treatment of PHN.

### RECOMMENDATIONS FOR CLINICAL PRACTICE

Tricyclic antidepressants are the drug of choice for PHN. Gabapentin, topical capsaicin, or oxycodone can be used for patients unable to tolerate tricyclic agents. In patients with severe, refractory pain from PHN, intrathecal methylprednisolone may provide relief.

*Karen L. Maughan, MD*  
*Department of Family Medicine*  
*University of Virginia Health System*  
*Charlottesville*  
*E-mail: kmaughan@virginia.edu*

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## Tissue adhesive works as well as suturing

Singer AJ, Quinn JV, Clark RE, Hollander JE. Closure of lacerations and incisions with octylcyanoacrylate: A multicenter randomized controlled trial. *Surgery* 2002; 131:270–6.

■ **BACKGROUND** Although suturing is the most common method of wound closure, it requires injection of an anesthetic, is time-consuming, carries the risk of a needle stick to the clinician, and requires a return visit for suture removal. Tissue adhesives applied to skin hold wound edges together and usually slough off within 5 to 10 days without requiring removal. This study compared an easy-to-use, topical adhesive, octylcyanoacrylate to standard wound closure methods (sutures, staples, or adhesive tapes).

■ **POPULATION STUDIED** This multicenter study enrolled 814 patients (924 wounds) from emergency departments, an urgent care clinic, outpatient surgery centers, and private practices. Patients had to be in good health (without insulin-dependent diabetes, peripheral vascular disease, bleeding diathesis, multiple trauma, or possibility of keloid formation) and older than 1 year. Wounds that could be repaired with 5-0 or smaller suture were eligible. Bites, puncture wounds, infected wounds, decubitus ulcers, stellate lacerations, wounds located on the vermilion border of the lip or mucosa, and wounds over flexor or extensor surfaces or near the eye were excluded. Seventy percent of the subjects were white and the mean wound length was approximately 2 cm.

■ **STUDY DESIGN AND VALIDITY** Eligible subjects were randomized using computer-generated random numbers and opaque envelopes (concealed allocation assignment) to receive either octylcyanoacrylate or standard wound closure. Although blinding patients or physicians to treatment was not possible, personnel assessing the outcomes at 3 months were blind to treatment group assignment. No baseline differences were noted between treatment

groups. Patients were analyzed in the groups to which they were randomized (intention-to-treat analysis) and follow-up was complete (96% at 1 week and 94% at 3 months). This study had adequate power (90%) to detect a difference (10%) in the proportion of patients with optimal wound appearance, but was underpowered to detect a small difference in infection or dehiscence rates.

■ **OUTCOMES MEASURED** The primary outcome measured was cosmetic wound appearance. Other outcomes included wound closure time, infection rates, and dehiscence rates.

■ **RESULTS** At 3 months no difference was noted in the percentage of wounds with optimal appearance (octylcyanoacrylate, 82% vs standard wound closure, 83%;  $P = .67$ ). Although wound closure with octylcyanoacrylate was faster than with standard wound closure (mean 2.9 vs 5.2 minutes,  $P < .001$ ), this small difference is probably not clinically significant. Infection rates were similar (octylcyanoacrylate, 2.1% vs standard wound closure, 0.7%;  $P = .09$ ), as were dehiscence rates (octylcyanoacrylate, 1.6% vs standard wound closure, 0.9%;  $P = .67$ ).

### RECOMMENDATIONS FOR CLINICAL PRACTICE

The tissue adhesive octylcyanoacrylate (Dermabond) is as effective as standard wound closure (sutures, staples, and tape adhesives) in repairing small uncomplicated lacerations and incisions (those that would normally be amenable to 5-0 suture) and does not lead to an increased rate of infection or dehiscence. Optimal cosmetic appearances at 3 months were no different for either treatment method. The decreased time and ease and safety of use favors a tissue adhesive.

*Brian T. Easton, MD  
Highlands Family Medicine  
Lebanon, Virginia  
E-mail: beaston@tangible.com*

## No benefit to adding warfarin to aspirin after heart attack

Fiore LD, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peducci P. Department of veterans affairs cooperative studies program clinical trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction. Primary results of the CHAMP study. *Circulation* 2002; 105:557-63.

■ **BACKGROUND** Aspirin alone, and warfarin alone, benefit survivors of acute myocardial infarction. However, it is not known whether combination therapy is more effective in preventing subsequent cardiovascular events.

■ **POPULATION STUDIED** Investigators enrolled 5059 patients from 78 VA medical centers, who were diagnosed with acute myocardial infarction. Screening was to be done within 14 days of the initial event. Exclusion criteria included life expectancy less than 2 years, active bleeding or risk of bleeding, treatment with high-dose aspirin or nonsteroidal anti-inflammatory drugs, other indications for anticoagulants, substance abuse, or living far from the medical center. Mean age was 64 years; 98% were men, 37% had history of previous myocardial infarction, 8% had prior congestive heart failure, 27% had diabetes mellitus, 55% had hypertension, and 45% were current smokers.

■ **STUDY DESIGN AND VALIDITY** This was a randomized, unblinded, controlled trial. After acute myocardial infarction, subjects were assigned to receive an antithrombotic therapy, either aspirin (162 mg daily) alone, or aspirin (81 mg daily) plus warfarin, adjusted to keep the international normalized ratio at 1.5 to 2.5. Delayed treatment was allowed for patients requiring invasive procedures. Hazard ratios were calculated to determine if a delay resulted in differences in mortality. An end-points committee, blinded to treatment assignment, adjudicated cause of death and major hemorrhage. The study was sufficiently large to detect a 15% reduction in annual mortality.

The methodologic strength of the study was fair. Major strengths included randomization and adequate power to detect a difference in the primary outcome. Subjects receiving combination therapy were seen regularly for titration of warfarin dose, in addition to the follow-up visits scheduled every 6 months for all subjects. Because of lack of blinding of subjects and clinical personnel, other than the end-points committee, this additional follow-up

could be an intervention in itself and could lead to measurement bias, or differential assessment of outcome that occurs for reasons other than the therapy being studied. An example would be differential assessment of incidence of bleeding by staff who regularly monitor international normalized ratios for one study group only.

■ **OUTCOMES MEASURED** The primary outcome measured was all-cause mortality; secondary outcomes included recurrent myocardial infarction, stroke, and major hemorrhage.

■ **RESULTS** There were 438 deaths (17.3%) in the aspirin group and 444 deaths (17.6%) in the combination group, after a median follow-up of 2.7 years. Recurrent myocardial infarction or stroke occurred in 13.1% and 3.5% of those taking aspirin and in 13.3% and 13.1% of those taking combination therapy, respectively. A delay in initiating treatment increased risk, although this risk was not significantly different between study groups. Fifteen percent of reported recurrent myocardial infarctions were not confirmed as such. Eighteen strokes that occurred in the aspirin group and 21 in the combination therapy group were not confirmed ischemic strokes. Major bleeding events per 100 patient-years of follow-up were 0.72 in the aspirin group and 1.28 in the combination therapy group, resulting in a statistically significant rate ratio of 1.78 (95% confidence interval [CI], 1.27-2.72), with the majority being gastrointestinal tract bleeding. The rate ratio for minor bleeding events was 4.63% (95% CI, 3.78-6.94). No difference was noted in the rate of confirmed intracranial hemorrhage between the 2 groups.

### RECOMMENDATIONS FOR CLINICAL PRACTICE

In patients with an acute myocardial infarction, the combination of low-dose aspirin and standard doses of warfarin, compared with aspirin alone, does not reduce all-cause mortality among a largely male patient population with a relatively high incidence of diabetes and hypertension. Moreover, aspirin monotherapy has a better safety profile than combination antithrombotic therapy.

*Pamela F. Blakely, MD  
Valerie J. King, MD, MPH  
Department of Family Medicine  
University of North Carolina at Chapel Hill  
Email: pamela\_blakely@med.unc.edu*